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VIA ECF

Honorable Tonianne J. Bongiovanni, U.S.M.J.
United States District Court
Clarkson S. Fisher Building & U.S. Courthouse
402 East State Street
Room 6052
Trenton, NJ 08608

Re: AstraZeneca vs. Hanmi, Civil Action No.: 11-760 (JAP) (TJB)

Dear Judge Bongiovanni:

This firm, along with Sughrue Mion, PLLC, represents the Hanmi Defendants in the above-referenced matter. We write in response to AstraZeneca's January 13, 2012 letter to the Court (D.I. 184) (requesting that certain portions of Hanmi's responsive *Markman* submissions be stricken) and the Court's instructions of January 17, 2012, directing this response.

Hanmi's responsive *Markman* submissions filed January 6, 2012 (D.I. 174, 175), were prepared in strict compliance with the Local Patent Rules, which govern the scope and content of the parties' *Markman* submissions. Local Patent Rule 4.5(c) provides that the parties "contemporaneously file and serve responding *Markman* briefs ***and any evidence supporting claim construction, including any responding experts' certifications or declarations***" within 60 days of opening *Markman* submissions. As set forth below, Hanmi's responsive submissions contained a Declaration and certain exhibits provided solely as rebuttal to new and expanded theories of claim construction provided by AstraZeneca -- long after the time for its required disclosure had passed (*i.e.* in the Joint Claim Construction Statement. (D.I. 92, 92-1 ("Joint Statement")). Hanmi could not have disclosed in the Joint Statement (filed September 14, 2011) evidence it did not know it would need as rebuttal until November 7, 2011 or December 7, 2011, the dates of AstraZeneca's Opening Brief (D.I. 133) and Dr. Davies' deposition. For this reason, Hanmi respectfully requests that AstraZeneca's motion be denied, as well as its request for relief in the alternative.

The Local Patent Rules clearly contemplate the submission of responsive declarations and supporting evidence with responsive *Markman* briefs, but nowhere do they contemplate a third round of *Markman* briefing, or a second round of depositions. Hanmi should not be prejudiced by the delay incurred by (1) AstraZeneca's initial failure to comply with Local Patent

Rule 4.3(b), and (2) its belated request to delay the *Markman* schedule pending its taking additional discovery and submitting an additional Declaration, which are not provided for by the Rules and which AstraZeneca chose not to timely submit.

Background

Presently, AstraZeneca seeks to have stricken exhibits 3-5, 7 and 8–13 of Hanmi's responsive *Markman* submissions, as well as the selected portions of the Supplemental Atwood Declaration (D.I. 184-1 (Ex. B)) and Hanmi's responsive brief (D.I. 184-1 (Ex. C)) designated by AstraZeneca. All of these exhibits and the statements citing to them in Hanmi's responsive brief and supporting declaration relate to the terms "alkaline salt" in the '504 patent and "pharmaceutically acceptable salt" in the '192 patent.

Argument

AstraZeneca Disclosed New Alkaline Salts For The First Time In Its Brief And Expert Testimony

Local Patent Rule 4.3(b) requires as part of the parties' Joint Statement identification of:

- *all* references from *the intrinsic evidence* that support that construction
- any *extrinsic evidence* ***known to the party*** on which it intends to rely either to support its proposed construction or to oppose any other party's proposed construction. L. Pat. R. 4.3(b) (emphasis added).

Because only extrinsic evidence ***known to the party*** **at the time of** the Joint Statement must be disclosed, the Rules clearly allow for the submission of rebuttal extrinsic evidence, *e.g.*, evidence not known or foreseen at the time of filing of the Joint Statement. In the Joint Statement, AstraZeneca identified seven extrinsic references supporting its proposed constructions of "alkaline salt" and "pharmaceutically acceptable salt." The '974 and EP 495 patents disclose the same six salt species as the '504 patent, plus the titanium salt and guanidinium salt; the three *Marie* references disclose the strontium salt; the Chambers Dictionary disclosed no salts; and the Berge reference was cited as "listing over twenty cations known to be used in salts fit for human consumption." (D.I. 92-1, p. 2). Substantively, the Berge reference lists 21 cations potentially useful in salt formation, 9 of which are metals and 12 of which are organic. (D.I. 112-4) (Many of the metal cations are the same as those listed in the '504 patent (Ca^{2+}, Li^{+}, Mg^{2+}, K^{+}, Na^{+}), while others are not.) Thus, as of the filing of the Joint Claim Construction and Prehearing Statement, Hanmi understood that AstraZeneca's "any basic salt" proposed construction would be supported by intrinsic and extrinsic evidence showing -- *at most* -- 20 or so salt species not disclosed in the '504 patent.

AstraZeneca's opening *Markman* brief (D.I. 133) went further, and broadened the types of salt species within the proposed scope of the claims to include "***at least***, the alkaline metals and alkaline earth metals," as well as "an ammonium group, which is an honorary alkaline salt." (D.I. 133, p. 12). In his supporting declaration, Dr. Davies stated that persons of ordinary skill

would understand that suitable cations for alkaline salt include "**at least**, cations of **all** of the metals in Groups I and II (lithium, sodium, potassium, **rubidium, caesium, beryllium**, magnesium, calcium, strontium or **barium**) as well as **ammonium**." (D.I. 133-3, ¶¶ 36-37 (emphasis added)). Nowhere prior to its opening *Markman* brief or Declaration in support did AstraZeneca disclose that **all** Group I and Group II elements, particularly rubidium, caesium, beryllium, barium (and honorary ammonium) were included within its proposed construction of "alkaline salt."

At his deposition, Dr. Davies went still further, stating that "the '504 patent covers **all** alkaline salts". . . ; "**All alkaline salts fulfill the criteria covered by the patent**" (D.I. 175-1 Davies Tr., p. 172); "Well, in principle, **all of the metals could form salts. And there are a lot of metals.**" (p. 160). Dr. Davies also explained that a number of organic salts would be within the scope of the proposed definition as well. (D.I. 175-1, Davies Tr. at 154-157 (formation of tetraalkyl ammonium salts); 158-159 (formation of pentamethyl guanidine, guanidinium salts)) and Exhibit 1, Davies Tr. at 241-242 (formation of some organic salts)). At no time prior to Dr. Davies' deposition did AstraZeneca disclose that *all metals* would be within the scope of AstraZeneca's proposed construction. The evidence referred to in the Joint Statement referred to -- at most-- the 5 metal species listed in the '504 patent, titanium, strontium, and 3 or 4 additional metals from the Berge reference.

Confronted with Astra Zeneca's clear decision to expand the scope of "alkaline salt" beyond what the originally cited extrinsic evidence supported, Hanmi was left with no choice but to present a focused response to several of the Group I and Group II salts about which it was never provided notice. At least Exhibits 3-5 and 7, ¶¶ 14 – 21 of the Supp. Atwood Decl. and pp. 3-4 of Hanmi's responsive brief address AstraZeneca's reliance on previously undisclosed beryllium, cesium, francium, radium, rubidium, and barium.[1]

AstraZeneca Also Put Forward A New Theory Not Previously Disclosed

AstraZeneca also urges that the correct construction of “alkaline” salt includes a limitation that they be "suitable for use in a pharmaceutical formulation." The extrinsic evidence AstraZeneca disclosed is referred to above. The three *Marie* articles relied on by AstraZeneca refer to the administration of various strontium compounds to laboratory mice and rats and say nothing about whether any of the compounds disclosed are suitable for use in a pharmaceutical formulation. Of the 21 cations in the Berge article disclosed as potentially useful, one third of them had not been approved in the U.S. and were only reported based on their use in other

[1] Dr. Davies testified at his deposition that, *e.g.*, thallium (a transition metal) would not be included within his definition of “alkaline salt” because it was toxic. (Ex. 1, Davies Tr. at 83, 173.) It would be a strange and manifestly unfair result if Dr. Davies could unilaterally reshape the contours of “alkaline salt” by discarding toxic thallium salts from AstraZeneca’s proposed definition, but Hanmi were not permitted to challenge those moving contours based on the toxicity of certain salt species on rebuttal, *the first opportunity it had to do so*. Hanmi's responsive submission highlights the toxicity of certain Group I and Group II salts, which is no more than Dr. Davies did at his deposition.

countries. (D.I. 112-4). Moreover, the Berge reference contained no disclosure of how to determine whether or not a salt was "suitable for use in pharmaceutical formulations," and specifically described toxicities associated with calcium, lithium, sodium, etc. salts. (D.I. 112-4, page 15 of Berge). None of the other references describe how to determine whether or not a particular salt was pharmaceutically acceptable.

Undaunted by the lack of clear guidance in the extrinsic evidence it cited, AstraZeneca posited for the first time in its opening *Markman* brief that since the claims were drawn to a 'pharmaceutical formulation' comprising an "alkaline salt," the term "pharmaceutical formulation" would be ***understood*** to limit "alkaline salts" to those salts suitable for use in a pharmaceutical formulation." (D.I. 133, p. 8.) Dr. Davies confirmed at his deposition that the "pharmaceutical acceptability" requirement was context-driven, based on the claims and the patent specification. (Ex. 1, Davies Tr., pp. 70-73.) As best understood, Dr. Davies' position is that "if an alkaline salt exists in a pharmaceutical formulation as claimed, the salt must *itself* be pharmaceutically acceptable." This theory was never disclosed in the Joint Statement and is most certainly not supported by any of the evidence AstraZeneca cited. At best, AstraZeneca's evidence can fairly be read to say that any potential salt would have to be studied to determine its suitability for use in a pharmaceutical formulation.

Faced with this new theory, Prof. Atwood provided an example of alkaline earth salts of a drug in a pharmaceutical formulation that were not *by themselves* pharmaceutically acceptable because of their high pH values in solution, but were formulated to be acceptable in a pharmaceutical preparation. As such, ¶ 40 of Prof. Atwood's Declaration is proper rebuttal to evidence newly raised by AstraZeneca and Dr. Davies well after the filing of the Joint Statement.

AstraZeneca Relied On New Evidence In Support Of "Pharmaceutically Acceptable Salt"

Finally, AstraZeneca proposed a construction of "pharmaceutically acceptable salt" that is the same as its proposed construction for "alkaline salt" in the Joint Statement (*e.g.*, "*a basic salt*. .."), and cited as part of its intrinsic evidence several portions of the '504 patent in support: Col. 2, l. 42 - Col. 3, l. 55; Col. 4, l. 51 -Col. 5 l. 1; Examples 1–7; claims 1–7, 10. (D.I. 92-1, p. 2). In its opening *Markman* brief, AstraZeneca stated that "the meaning of 'pharmaceutically acceptable salt' in the '192 patent claims is **the same as** that for 'alkaline salt in the '504 patent claims" (D.I. 133, p. 21), but went further, arguing that:

- in the context of the '504 patent, the ordinary meaning of "alkaline salt" is a salt of esomeprazole ***that is generated under basic or alkaline conditions*** (D.I. 133 p. 12).
- alkaline salts were surprisingly stable under alkaline conditions, "***as contrasted to the acidic conditions employed in prior art in unsuccessful efforts to prepare 'optically pure [individual enantiomers of] omeprazole***.'" (D.I. 133, p. 22).

In support of its argument, AstraZeneca cited Col. 13, l. 31 -- Col. 14, l. 4 -- Col. 1, ll. 27–42 of the '504 patent, which specifically described the prior art preparation of omeprazole under acidic conditions in the DE 455 patent ("the Kohl reference"). But that portion of the '504 patent was never disclosed by AstraZeneca in the Joint Statement as intrinsic evidence upon which it intended to rely. (D.I. 92-1, p. 2 ("alkaline salt" in the '504 patent) and p. 25 ("pharmaceutically acceptable salt" in the '192 patent)). AstraZeneca first raised the '504 patent discussion of the Kohl reference in its opening brief to support its argument that acidic conditions could not be used to prepare omeprazole. Dr. Davies augmented the arguments made in AstraZeneca's opening brief, stating that there was no evidence that the authors of the Kohl reference were able to obtain optically pure enantiomers of omeprazole at all. (Ex. 1. Davies Tr., pp. 145-146). Prof. Atwood's statements in ¶¶ 50-51 of his Supplemental Declaration provide a focused response to AstraZeneca's newly minted *but factually incorrect* statement that the prior art did not show how to produce optically pure enantiomers of omeprazole under acidic conditions. Because Hanmi had no advance notice of this new argument or of the intrinsic evidence AstraZeneca would rely on in support of it, Hanmi could not have disclosed its opposing evidence in the Joint Statement, and therefore Prof. Atwood's comments constituted proper rebuttal.

All Of AstraZeneca's Arguments And Positions Concerning Acid Salts Were Raised For The First Time In Its Opening Submissions

AstraZeneca's opening submissions suggested for the first time ever that acid salts of esomeprazole could not be formed, despite the '192 patent's express definition of "pharmaceutically acceptable salt" at D.I. 111-9 at column 4, lines 13-16 (both acid and alkaline pharmaceutically acceptable salts).[2] *See* D.I. 133, pp. 9, 17-18. No paper in this case, including the Joint Statement, ever contained arguments or evidence purporting to claim that acid salts could not be formed, would not be stable, or were inoperative. Therefore, Hanmi was fully justified in establishing that acid salts of esomeprazole could easily be formed, based in part on AstraZeneca's own prior art patents describing acid salts of, *e.g.*, omeprazole. AstraZeneca's arguments that any acid salt rebuttal is improper are specious.

Paragraphs 53-56 of the Supplemental Atwood Declaration and the single sentence in Hanmi's responsive brief summarizing those paragraphs (D.I. 174, p. 17) refer to literature examples disclosing acid salts of omeprazole. One reference in particular is AstraZeneca's own prior art '257 patent, which lists a number of possible acid salts of, *e.g.*, omeprazole. As such, each of these portions of Hanmi's responsive submissions are proper rebuttal to statements and theories raised for the first time by AstraZeneca *after* the filing of the Joint Statement.

[2] In contrast, Dr. Davies' Declaration stated that "(–)-omeprazole is 'amphoteric,' which means that it is able to form a salt either under basic conditions by loss of a proton or under acidic conditions by addition of a proton." (D.I. 133-3, Davies Decl., ¶¶ 38-40 at pp. 11-12.) Dr. Davies even provided an illustration of how an acid salt of (-)-omeprazole could be formed. *Id.* at ¶ 40. At his deposition, however, Dr. Davies testified that he was not aware of the preparation of any acid salts of either (-)-omeprazole or omeprazole, and that he would not expect them to be stable. (Ex. 1, Davies Tr., pp. 125-127.)

Because all of the references and portions of Hanmi's responsive *Markman* submissions that AstraZeneca now seeks to strike were based on new evidence (intrinsic or extrinsic) never disclosed in the Joint Statement, Hanmi could not have disclosed its responsive evidence at the time of filing of the Joint Statement. Hanmi's responsive submission complied with Local Pat. Rule 4.3(c) and constituted proper rebuttal; as a result, AstraZeneca's motion should be denied.[3]

Given Hanmi's showing that its responsive submissions were entirely proper rebuttal to new evidence, arguments, positions and theories raised for the first time in AstraZeneca's opening submissions, it is clear that the present tactic is simply one of attempted delay. The record is clear that AstraZeneca never previously mentioned all Group I and Group II metals as suitable cations; Hanmi had every right to establish the toxicity and inoperability of some of them as rebuttal. AstraZeneca never argued the inoperability of acid salts of esomeprazole until its opening submissions; Hanmi again had every right to establish in rebuttal that AstraZeneca was plainly wrong based on AstraZeneca's own prior art patents. The same is true for the other new evidence, positions and theories raised for the first time in AstraZeneca's opening submissions.

AstraZeneca knows well that delaying the *Markman* hearing could well delay the ultimate resolution of this case because the balance of the case schedule remains to be set following the Court's *Markman* rulings. Judicial economy and principles of fundamental fairness would be frustrated if AstraZeneca's unsupported pleas for additional *Markman* briefing were countenanced. Hanmi respectfully asks that no additional *Markman* briefing or discovery be permitted and that the hearing date be scheduled at the Court's earliest convenience as requested in Hanmi's January 13, 2012 letter.

Respectfully,

/s/ Allyn Z. Lite

Allyn Z. Lite

AZL:emp

cc: Hon. Joel A. Pisano, U.S.D.J. (via ECF)
All Counsel of Record (via ECF)

[3] *Hoffman-LaRoche Inc. v. Apotex.*, C.A. No. 07-4417, D.I. 397 (D.N.J. Dec. 29, 2011), relied upon by AstraZeneca in support of the present motion, is irrelevant both factually and legally.